REMARKS

Applicants have cancelled claim 27. Applicants have amended claim 24. The amendment to claim 24 is supported throughout the specification, for example, at paragraphs [0018], [0033]-[0038] and [0116]. Applicants have also added new claim 28. Support for claim 28 can be found throughout the specification, for example, in original claim 24 and paragraphs [0087]-[0088].

Accordingly, Applicants submit that no new matter has been added by virtue of these amendments or the new claim, and their entry is respectfully requested.

The Examiner rejected claims 24, 26, and 27 as allegedly being obvious over US Patent Application Publication 2002/0115665A1 to DePetrillo *et al.* ("DePetrillo"). Specifically, the Examiner argued that DePetrillo teaches administration of calpain inhibitors (HIV protease inhibitors) to patients that are exposed to calpain mediated physiological damage such as **thrombotic platelet aggregation** (paragraph 6). Although the Examiner acknowledged that DePetrillo does not specifically recite "fibrinolysis," the Examiner contended that "the doses administered in the instant case capable of promoting fibrinolysis are from 5 to 1000 mg (paragraph 103) which partially overlaps with the doses recited in the treatment of DePetrillo from 300 to 2400 mg."

Applicants respectfully disagree and submit that the rejection should be withdrawn for the following reasons.

Although the Examiner acknowledged that the prior art does not teach the claimed method, the Examiner argued that an individual who is the subject of DePetrillo might also have thrombi and in that case, would inherently be treated. Applicants have amended claim 26 to make explicit that which was implicit, namely, that the method is not being used randomly to any individual. Rather, it is being used in a subject who has been diagnosed as having a thrombus or as being at risk for thrombus formation. Patient selection in such a manner is not taught or suggested by DePetrillo. Moreover, DePetrillo is directed to treating conditions associated with calpain activation and it is not directed to a patient being treated with an anti-platelet, anti-coagulation, or anti-thrombotic agent as required by claim 28.

More specifically, it is well known that platelet agglutination and prevention of thrombus formation involve completely different biological phenomena and pathways than fibrinolysis and

dissolving of an existing thrombus. Fibrinolysis refers to a process by which an existing and fully-formed clot is broken down by enzymes, such as plasmin, to form fibrin degradation products. In fact, the process of fibrinolysis is actively inhibited by the presence of platelets, which secrete molecules, such as plasminogen activator inhibitors, which prevent the conversion of plasminogen to the active enzyme plasmin, and thus the lysis of fibrin to its degradation products. To support the facs discussed above, Applicants attach herewith Exhibit A, Furie *et al.*, NEJM 2008, 359:938-949, and Exhibit B, Rijken and Lijnen, J Thromb Haemost. 2009, 7(1):4-13.

In contrast, thrombus formation is a two-step process, that occurs via the aggregation of platelets followed by the activation of the humoral coagulation system. Platelet agglutination occurs when platelets are activated as a consequence of endothelial damage. Platelet agglutination thus constitutes the first step that can result in blood coagulation and clot formation and is known as primary hemostasis. Platelet aggregation by itself does not lead to clot formation, as this requires the activation of the coagulation cascade (secondary hemostasis) by either the intrinsic or extrinsic pathways, to form fibrin strands, which ultimately results in the formation of a clot. The formation of a clot in a blood vessel is termed a thrombus (see, e.g., Exhibits A and B).

Further, Applicants submit that prior to the instant invention, an *in vitro* method to determine whether a given compound or agent has fibrinolytic activity, i.e., the ability to dissolve a clot, *in the presence of platelets*, as occurs *in vivo*, was simply not available. In fact, the clot lysis assay described in the instant application from paragraphs [0116]-[0122] represents the first demonstration of successful clot lysis in the presence of platelets. Thus, prior to the instant invention, a skilled artisan would not have had any way of determining whether an agent, such as a syk or calpain inhibitor, could be used in the instantly claimed *in vivo* method of promoting fibrinolysis and dissolving a thrombus.

Accordingly, references to prevention of thrombotic platelet aggregation refer to a completely different phenomenon compared to fibrinolysis of existing thrombi, and involve completely different factors and pathways, some of which act in opposition to each other. Thus, Applicants submit that a reference to an anti-thrombotic effect should not be confused with the ability to modulate fibrinolysis.

DePetrillo does not teach or even suggest a specific advantage of a calpain inhibitor in a method for **dissolving an existing clot**, *i.e.*, a thrombus. The DePetrillo passages referred by the Examiner (paragraphs 6, 106, and 113) do not teach or suggest that the administration of a calpain inhibitor can dissolve an existing thrombus. Accordingly, a skilled artisan reading the DePetrillo reference and without additional data could not conclude that inhibition of calpain activity can be used to promote fibrinolysis of a thrombus. Only after reading the specification, which teaches that inhibition of calpain results in fibrinolysis, even in the presence of platelets, and which provides working examples using exemplary calpain inhibitors to demonstrate that the addition of a calpain inhibitor increases fibrinolysis of a pre-formed clot, would one be able to understand this novel use for calpain inhibitors. Moreover, based on the teachings of DePetrillo, one of ordinary skill in the art could not have even expected the calpain inhibitor therapy to work because there is no reference of these agents being capable of dissolving an existing thrombi, and no assay existed to assess whether an agent had such an activity.

Accordinly, Applicants respectfully submit that the rejection of claims 24 and 26 under 35 U.S.C. § 103(a) over DePetrillo should be withdrawn. Applicants have cancelled claim 27 rendering the rejection moot with respect to claim 27.

The Examiner rejected claims 24, 25, and 27 as allegedly being obvious over US Patent No. 6,432,963 B1 to Hisamichi et al. ("Hisamichi"). Specifically, the Examiner contended that Hisamichi teaches a pyrimidine-5-carboxamide derivative having Syk tyrosine kinase inhibition activity (column 1, lines 5-8) for **treatment of diseases in which platelet agglutination takes part such as thrombosis** and the like (column 13, lines 36-38). While the Examiner acknowledged that Hisamichi **does not teach promotion of fibrinolysis**, the Examiner contends that the doses administered partially overlap with the doses recited in the treatment of Hisamichi who teaches about 0.001 to 100 mg/kg (column 16, lines 27-30).

Applicants respectfully disagree and submit that the rejection should be withdrawn for the following reasons.

The claims have been amended to make explicit that the method is being used on an individual diagnosed as having an existing thrombus or thrombi. Like DePetrillo, also Hisamichi does not teach a specific advantage or property of a Syk inhibitor in a method for **dissolving clots**. Hisamichi only recites a list of diseases that includes those "in which **platelet**

agglutination takes part." The Hisamichi reference does not teach or suggest a method to **promote fibrinolysis** or the dissolving of a clot using Syk inhibitors, as recited in the instant claims. As explained above, platelet agglutination and fibrinolysis are distinct biological processes, involving completely different pathways. Further, no assay existed to determine whether an agent had fibrinolytic activity in the presence of platelets.

Thus, Applicants respectfully submit that reading the vague reference to diseases "in which platelet agglutination takes part" as a potential use for Syk tyrosine kinase inhibition would not motivate or suggest to one of skill in the art that such inhibition would be effective in the actual dissolution of a thrombus, *i.e.,* fibrinolysis. In contrast, the instant specification discloses that inhibition of Syk can lead to actual fibrinolysis, even in the presence of platelets, and provides working examples using exemplary Syk inhibitors to demonstrate that the addition of a Syk inhibitor increased fibrinolysis of a pre-formed clot.

In view of the above, Applicants respectfully submit that the rejection of claims 24 and 25 under 35 U.S.C. § 103(a) over Hisamichi should be withdrawn. Applicants have cancelled claim 27 rendering the rejection moot with respect to claim 27.

In view of the foregoing, Applicants submit that all issues raised in the Office Action have been addressed herein. Early and favorable action is earnestly solicited.

The Commissioner is hereby authorized to charge fee deficiencies or credit overpayments associated with the instant filing in above-referenced matter to NIXON PEABODY LLP Deposit Account No. 50-0850.

Date: November 6, 2009

Respectfully submitted,

/Leena H. Karttunen/

Customer No.: 50607

Ronald I. Eisenstein (Reg. No. 30,628)
Leena H. Karttunen (Reg. No. 60,335)
Nixon Peabody LLP
(617) 345-6054 / 1367